REMARKS

This Amendment is being filed under 37 C.F.R. §1.116 governing Amendment After Final Rejection. This Amendment is appropriate for entry under Rule 116, since it does not raise new issues and places the application in allowable condition and/or places the application in better condition for appeal.

There have been no amendments made to the specification or drawings. New claim 25 has been added. New claim 25 is identical to originally filed claim 9. Applicant notes that claims 20-23 were previously cancelled without prejudice and claims 1-8 and 15-20 were previously withdrawn, under traverse, from consideration based on a restriction of invention. Upon entry of this amendment, claims 1 – 19, 24 and 25 will be pending in the application.

Applicant Includes Additional Materials In Response to Examiner Comments

In response to the Examiner's statement as to the clarity of the phrase "lysosomal storage disorders"[1], Applicant includes with this response:

1. Front page of United States Patent No. 5,798,366 titled Method for Treatment of CNS-Involved Lysosomal Storage Diseases.
2. Front page of United States Patent No. 6,583,158 B1 titled Method for Enhancing Mutant Enzyme Activities in Lysosomal Storage Disorders.
3. A printout of the result page from an NCBI global database search for the synonymous phrase "lysosomal storage disease". Applicant notes that the phrase appears in numerous databases.
4. A printout of Pub-Med search results, first 100, for the phrase "lysosomal storage" in the publication title and limited to publications having a publication date prior to October 28, 2001. Applicant notes that 338 publications contain "lysosomal storage" in the title where it is used with other terms, for example, disease, disorder, and defect.

[1] "[a]s far as "lysosomal storage disorders" go, they also are not enabled and cannot be determined as to what they would do. Applicant has claimed two specific disorders (Alzheimer's and Parkinson's) but it is not clear what would encompass "lysosomal storage disorders". Without more the claims are simply not enabled by the specification"

5. FDA approved label for Aldurazyme® (laronidase) and toxicologist report indicating that the drug is indicated for a lysosomal storage disease.

In response to the Examiner's statement and question as to treatments for Alzheimer's and Parkinson's disease[2], Applicant includes with this Response:

1. Partial copies of United States Patent Nos. 6,448,270; 6,274,606; 6,232,316; 6,469,055; 6,277,874; 6,451,797; 6,632,962; 6,509,363; 6,624,162; 6,617,358; 6,133,306; 6,184,248; 6,787,564; 6,562,813; 6,486,194; 6,653,310; 6,680,317and 6,566,387 which all are directed to the treatment of Alzheimer's and/or Parkinson's disease.
2. Partial copy of the minutes from the March 13, 2001 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Applicant notes that Dr. Katz from the FDA stated at this meeting that the "Federal Food, Drug and Cosmetic Act, which is the statute under which we regulate drugs, requires that in order for a new drug to be approved the sponsor must submit what is called substantial evidence of effectiveness that the treatment will have the effect represented for it in the product labeling.... As you probably know, currently there are four approved treatments for Alzheimer's disease..."
3. National Institute of Health, Clinical Trial notice, identifying a phase II study for "treatment of persons with possible or probable Alzheimer's disease".
4. A portion of FDA Talk Paper T04-09 which discusses approval of apomorphine for Parkinson's patients and mentions that there are "standard Parkinson's drug treatments".
5. News release identifying memantine HCl as approved by the FDA for treatment of Alzheimer's disease.

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[2] "Applic ant argues that Alzheimer's or Parkinson's have known treatments but are they really effective? The key word is "tre ating". How can one treat such diseases such as Alzheimer's or Parkinson' s if one does not show results *in vivo* that such compounds claimed effectively treat the claimed disease. The articles submitted only state that treatments are being tested or speculate that they work, but there is nothing that shows that they effectively threat the diseases such as Alzheimer's and Parkinson's ."

6. News release identifying galantamine HBr as approved by the FDA for treatment of Alzheimer's disease.
7. News release identifying rivastigmine tartrate as approved by the FDA for treatment of Alzheimer's disease.
8. News release identifying donepezil HCL as approved by the FDA for treatment of Alzheimer's disease.
9. News release identifying entacapone as approved by the FDA for treatment of Parkinson's disease.
10. FDA approved label for Exelon® (rivastigmine tartrate), indicated "for the treatment of mild to moderate dementia of the Alzheimer's type".
11. FDA approved label for Aricept® (donepezil HCl), indicated "for the treatment of mild to moderate dementia of the Alzheimer's type".
12. FDA approved label for Stalevo® (carbidopa, levodopa and entacapone), indicated "to treat patients with idiopathic Parkinson's disease".

Claim Rejections Under 35 U.S.C. §112 First Paragraph.

Claims 9-14 and 24 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

- **The legal burden necessary to properly assert a 35 U.S.C. §112, first paragraph rejection.**

35 U.S.C. section 112, first paragraph reads:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best way contemplated by the inventor of carrying out his invention.

Additionally, the courts have interpreted the enablement requirement to require that the specification teach those in the art to make and use the invention without "undue experimentation". As set out in In re Wands, 858 F.2d 731, 737; 8 USPQ2d

1400, 1404 (Fed. Cir. 1988), factors to be considered in determining whether required experimentation is undue include:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of a person of ordinary skill;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples in the specification; and
8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The courts have pointed out that "[n]ot every last detail [of an invention need] be described [in a patent specification], else patent specifications would turn into production specifications, which they were never intended to be." In re Gay, 135 USPQ 311,316 (C.C.P.A. 1962). Citing the opinion in Gay, the Board of Patent Appeals and Interferences echoed this point in its statement that " the law does not require a specification to be a blueprint to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph," Staehelin v. Secher, 24 USPQ2d 1513, 1516 (Bd. Pat. App. & Int. 1992). Even more broadly, the MPEP states the specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public. See MPEP section 2164.05(a).

The United States Patent and Trademark Office recognizing the above legal authority has promulgated Training Materials For Examining Patent Applications With Respect To 35 U.S.C. 112, First Paragraph-Enablement Chemical/Biotechnical Applications. As stated in these training materials at section III, paragraph 6, with bolding added:

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above [Wands] factors while ignoring one or more of the others. The examiner's analysis **must** consider all the evidence related to each of these factors, and any conclusion of non-enablement **must** be based on the evidence as a whole.

- **The Office communication assertions concerning enablement.**

The Office Communication, mailed November 5, 2004, asserted on page 3 that:

> The claims are not enabled for treating Alzheimer's, Parkinson's or lysosomal disorders. There is no known cure for treating Alzheimer's or Parkinson's thus treating is also not known. No known treatment can keep the disorders from happening. In fact, many people in the United States alone have such ailments and never get better. The evidence on record does not show that one who has such ailments ever gets any better, so how can one claim such treatments when they do not do what they claim they do? Without scientific data showing the diseases are prevented or cured then the treatment of diseases is just unknown since patients with such diseases never get any better.
>
> As far as "lysosomal storage disorders" go, they are also not enabled and cannot be determined as to what they would do. Applicant has claimed two specific disorders (Alzheimer's and Parkinson's) but it is not clear what would encompass "lysosomal storage disorders". Without more the claims are simply not enabled by the specification.
>
> Applicant argues that Alzheimer's and Parkinson's have known treatments but are they really effective? The key word is "treating". How can one treat such dieases such as Alzheimer's or Parkinson's if one does not show results *in vivo* that such compounds claimed **effectively** (bolding original) treat the claimed disease[3]. The articles submitted only state that treatments are being tested or speculate that they work, but there is nothing that shows that they **effectively** (bolding original) treat the diseases such as Alzheimer's and Parkinson's.

This is apparently the entirety of the Office communication rejection under 35 U.S.C. §112, first paragraph.

- **The Office communication assertions do not meet the required legal burden to assert a 35 U.S.C. §112, first paragraph rejection.**

Applicant notes that in properly rejecting claims under 35 U.S.C. §112, first paragraph the Examiner:

> . . . bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the

[3] Applicant respectfully reminds the Examiner that treatment claims do not necessarily require a showing of *in vivo* efficacy to be enabled. See, e.g., Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 748 (Fed. Cir. 1985).

> specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.
> In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

In addition, as discussed above the United States Patent and Trademark Office has stated that (bolding added): "It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above [Wands] factors while ignoring one or more of the others. The examiner's analysis **must** consider all the evidence related to each of these factors . . ."

- The Office communication NEVER considers or discusses ANY of the Wands factors at all.
- The Office communication NEVER considers or discusses how the evidence relates to ANY of the Wands factors.

Therefore, the Applicant reasserts the traversal and request made in the August 17, 2004 Response to Office Action in which the Applicant respectfully traversed the above rejection under 35 U.S.C. §112, first paragraph and requested that it should be explicitly withdrawn. Furthermore, the Applicant again requests that if the Examiner maintains a rejection under 35 U.S.C. §112, first paragraph, then the Examiner should include an analysis applying ALL of the Wands factors to Applicant's specification and the art in this area. Claims 9-14 and 24 are patentable for at least the reason that the Examiner has failed to properly reject these claims under 33 U.S.C. §112, first paragraph.

- **The Office communication assertions are contrary to knowledge in the art.**

The Office communication rejection appears to center around the position that: "[t]here is no known cure for treating Alzheimer's or Parkinson's thus treating is also not known." More simply, the Office communication appears to assert that cure = treatment.

The Office position appears to be misplaced, incorrect, and fundamentally lacking technical support. There are a number of diseases for which no cure is known

but for which treatment is possible. For example, diabetes cannot be cured, however diabetics can be treated with diet or insulin. As another example HIV cannot be cured, however drugs are available to treat the disease. Thus, it is beyond argument that a disease can be treated even if that same disease cannot be cured. Applicant includes, as further support for this position, partial copies of United States Patent Nos. 6,605,589; 6,512,003; 6,432,941; 6,251,882; 6,727,265; 6,797,721; 6,743,786; and 6,274,606 which are directed toward treating such disease states as Alzheimer's, Parkinson's, cancer, and human immunodeficiency virus. Applicant notes that these patents rely on only *in vivo* data.

The Office position with regard to treatments for, at least, Alzheimer's is also misplaced, incorrect and fundamentally lacking technical support. This is evidenced by the plethora of known treatments for this disease. For example, the United States Food and Drug Agency (FDA) specifically stated, as early as 1992, that there are "**[s]everal compounds for the treatment of Alzheimer's disease are under development or testing**. (emphasis added)" FDA's ALZHEIMER'S DISEASE UPDATE, T92-43, page 1, Sept. 24, 1992, (copy previously submitted). Furthermore, on September 9, 1993 the Food and Drug Administration approved a drug "**specifically to treat symptoms of Alzheimer's disease** (emphasis added)" and distinguished the term "treatment" from the term "cure" in stating the approved drug was "not a cure for Alzheimer's disease". FDA Press Release, P93-37, September 9, 1993 (copy previously submitted). Applicant further notes that as discussed by Dr. Katz in the March 13, 2001 meeting minutes of the Peripheral and Central Nervous System Drugs Advisory Committee (copy enclosed) the "Federal Food, Drug and Cosmetic Act, which is the statute under which we regulate drugs, requires that in order for a new drug to be approved the sponsor must submit what is called **substantial evidence of effectiveness that the treatment will have the effect represented for it in the product labeling** (emphasis added)...." With regard to Dr. Katz's statement, the Applicant directs the Examiner's attention to the FDA approved labels (copies enclosed) for Exelon® and Aricept® both of which are indicated "for the treatment of mild to moderate dementia of the Alzheimer's type". Unequivocally these labels demonstrate to the Examiner that effective treatments

for disease conditions such as Alzheimer's exist. As such, the Examiner must withdraw the rejection under 35 U.S.C. §112, first paragraph.

With regard to Parkinson's disease, Applicant directs the Examiner's attention to a published article[4] (copy previously submitted) which clearly indicates that as early as, at least, 1998 there existed a "**primary treatment for PD (Parkinson's Disease)** (emphasis added)". Based on at least this showing the Examiner's asserted position with regard to the nonexistence of treatments for Parkinson's disease appears to be in clear error. In addition, and with regard to Dr. Katz's statement above, the Applicant directs the Examiner's attention to the FDA approved label (copy enclosed) for Stalevo® (carbidopa, levodopa and entacapone), indicated "to treat patients with idiopathic Parkinson's disease". Unequivocally this label demonstrates to the Examiner that effective treatments for disease conditions such as Parkinson's exist. Claims 9-14 and 24 have been improperly rejected under 35 U.S.C. §112, first paragraph, for at least these reasons.

- **Applicant's claims reciting Lysosomal Storage Disorder are enabled.**

The Examiner has stated that "[a]s far as "lysosomal storage disorders" go, they are not enabled and cannot be determined as to what they would do." Applicant respectfully reminds the Examiner that "[p]atent documents are written for persons familiar with the relevant field; the patentee is not required to include in the specification information readily understood by practitioners, lest every patent be required to be written as a comprehensive tutorial and treatise for the generalist, instead of a concise statement for persons in the field. Thus resolution of any ambiguity arising from the claims and specification may be aided by extrinsic evidence of usage and meaning of a term in the context of the invention." Verve, LLC v. Crane Cams, Inc., 311 F.3d 1116, 1119, 65 USPQ2d 1051 (Fed. Cir. 2002); See Bayer AG v. Schein Pharmaceuticals, Inc., 301 F.3d 1306, 1314, 64 USPQ2d 1001 (Fed. Cir. 2002) ("Because an enabling disclosure by definition turns upon the objective understanding of a skilled artisan, the

[4] Altered Thalamic Response to Levodopa in Parkinson's Patients With Dopa-induced Dyskinesias,

enablement requirement can be met by reference to the knowledge of one of ordinary skill in the relevant art."); S3 Inc. v. nVIDIA Corp., 259 F.3d 1364, 1371, 59 USPQ2d 1745 (Fed. Cir. 2001) ("The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention).

The Applicant respectfully asserts that the application, as filed, clearly enables the claim since it is well known that lysosomal disruption is associated with, among other things, the intracellular build up of protein fragments and aggregates which in turn are associated with neurodegenerative disorders. Specification, page 1, paragraph 2. In support of this assertion and as discussed by the courts, "the enablement requirement can be met by reference to the knowledge of one of ordinary skill in the relevant art". Bayer AG, at 1314 (Fed. Cir. 2002).

Applicant has therefore enclosed with this paper several additional documents[5] in addition to the several publications[6] previously submitted. These documents and publications clearly identify that the phrase "lysosomal storage disorder" was well known in the art at the time the application was filed. Applicant notes that one reference, published in 1998, states that lysosomal storage disorders had been known for at least "a quarter of a century"[7] This reference specifically discusses the effect lysosomal storage disorders have on the intracellular accumulation of metabolic products. One skilled in the relevant art would understand what was encompassed by the phrase "lysosomal storage disorder" and would find the Applicant's specification to provide adequate guidance on how to use the claimed compositions. For example, the Applicant directs the Examiner's attention to at least Example 8 on page 19 of the

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Tamara Hershey et al. Proc. Natl. Acad. Sci. USA, Volume 95, pp 12016-12021, (September 1998)

[5] Applicant directs the Examiner's attention to the previous section titled Applicant Includes Additional Material in Response to Examiner Comments.

[6] Gene Therapy of Lysosomal Storage Disorders, A. Salvetti, J. M. Heard, O. Danos, British Medical Bulletin, Vol. 51, No. 1, 106-122 (1995); Prevalence of Lysosomal Storage Disorders, Peter J. Meikle et al. , Jama, Vol. 281, No.3, 249-254 (1999); Cellular Pathology of Lysosomal Storage Disorders, Sidney Weisner, Rose F. Kennedy, Brain Pathology, vol. 8, 175-193 (1998). See also citation and abstracts of 48 items obtained from a search of PubMed for publications prior to the application' s filing date having "lys osomal storage disorders" in the title.

[7] Cellular Pathology of Lysosomal Storage Disorders at page 175.

specification. As such, Applicant respectfully requests that the rejection of the claims based on the language "lysosomal storage disorders" be withdrawn. Claims 9-14 and 24 are patentable for at least this reason.

- **The enablement of Applicant's claims is supported by FDA labeling.**

Applicant directs the Examiner's attention to the FDA approved label (copy enclosed) for Aldurazyme® (laronidase) and the toxicologist report indicating that the drug is indicated for a lysosomal storage disease. In light of Dr. Katz's above statement this label and report unequivocally demonstrate to the Examiner that effective treatments for conditions such as lysosomal storage disorder exist. As such, the Examiner must withdraw the rejection under 35 U.S.C. §112, first paragraph.

- **The enablement of Applicant's claims is supported by more recent scientific investigation.**

In one embodiment Applicant's invention enhances lysosomal function using a lysosomal modulating compound. Applicant previously submitted the cover page from an article published by the Journal of Neuroscience in 2004[8]. The abstract of this article states that: ". . . enhancing lysosomal function may be a potential therapeutic strategy to halt or even prevent the pathogenesis of Parkinson's disease and other Lewy body diseases." Thus, there is scientific evidence published in medical journals supporting the enablement of Applicant's claims. Claims 9-14 and 24 are patentable for at least this reason.

- **Applicant respectfully requests that the Examiner produce a Personal Knowledge Affidavit or Declaration.**

The Examiner, as discussed above, has based the rejection of claims 9-14 and 24 on the factual assertion that "treating (Alzheimer's or Parkinson's) is also unknown". Applicant has submitted copies of statements from the FDA showing the Examiner's

[8] Clearance of alpa-Synuclein Oliugomeric Intermediates via the Lysosomal Degradation Pathway, He-Jin Lee, Farnaz Khoshaghideh, Smita Patel and Seung-Jae Lee, The Journal of Neuroscience, 24(8):1888-1896 (February 25, 2004).

statement to be in clear error. However, the Applicant assumes that the Examiner must have been aware of, at the time the May 18, 2004 and November 5, 2004 Office Actions were mailed, the Administrative Procedure Act (APA) which requires that the Examiner apply a "substantial evidence" standard of review when relying on "common knowledge in the art or well known prior" See MPEP 2144.03. As such, the Examiner's statement must be backed by adequate evidence, which supports a finding that treatment of Alzheimer's is unknown. Since the Examiner has not provided the Applicant with documentary evidence, the Applicant assumes that the rejection must be based on the Examiner's personal knowledge. As discussed in the MPEP at §2144.03 (C) the Examiner should "provide an affidavit or declaration setting forth specific factual statements and explanation to support" his finding that treatment for Alzheimer's is unknown.

- **Applicant Requests Withdrawal of the Rejection if Examiner Fails to Provide Substantial Evidence.**

If the Examiner is unable to provide the required affidavit or declaration supporting a finding that a treatment of Alzheimer's is unknown, Applicant respectfully requests that the rejection of claims 9-14 and 24 be explicitly withdrawn. Applicant's basis for this request rests on, at least, the grounds that the examination has failed to comport with 37 C.F.R. §1.104 Nature of Examination, which reads in one pertinent portion:

> (a) Examiner's action. (1) On taking up an application for examination or a patent in a reexamination proceeding, the Examiner shall make a thorough study thereof and shall make a thorough investigation of the available prior art relating to the subject matter of the claimed invention. The examination shall be complete with respect ...to the patentability of the invention as claimed (emphasis added), as well as with respect to matters of form, unless otherwise indicated.

- **Applicant's Concern With Regard to Examiner's Final Rejection of the Claims**

Applicant notes with extreme concern that the Examiner has appeared to disregard MPEP §706.07 which relates to Final Rejection and which reads in one

pertinent portion:

> Before final rejection is in order a clear issue should be developed between the Examiner and Applicant. To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the Applicant and the public, the invention as disclosed and claimed should be thoroughly searched in the first Office Action and the references fully applied...
>
> The Applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the Examiner to that end, and not be prematurely cut off in the prosecution of his or her case... The Examiner should never lose sight of the fact that in every case the Applicant is entitled to a full and fair hearing, and that a clear issue between Applicant and Examiner should be developed, if possible, before appeal ...
>
> In making the final rejection, all outstanding grounds of rejection of record should be carefully reviewed, and any such grounds relied on in the final rejection should be reiterated. They must also be clearly developed to such an extent that Applicant may readily judge the advisability of an appeal unless a single previous Office Action contains a complete statement supporting the rejection....

Applicant notes that the Examiner has failed to address numerous points made in Applicant's previous Response to Office Action, for example, request to provide substantial evidence.

Claim Rejections Under 35 U.S.C. §112 Second Paragraph.

Claims 9-14 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite or failing to particularly point and distinctly claim the subject matter which the Applicant regards as the invention. Specifically, the Examiner has stated that [I]t is not clear what is meant by the term, "lysosomal storage disorders".

Applicant notes that "the test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification" Miles Laboratory, Inc. v. Shandon Inc., 997 F.2d 870 (Fed. Cir. 1993), cert. denied, 510 U.S. 1100 (1994). It is clear, as previously discussed, what the bounds of the claim

language "lysosomal storage disorders" encompass when read in light of the specification. Clearly one skilled in the relevant art would understand the term "lysosomal storage disorders" and bounds of the claims when read in light of the specification as evidenced by references such as: Gene Therapy of Lysosomal Storage Disorders, A. Salvetti, J. M. Heard, O. Danos, British Medical Bulletin, Vol. 51, No. 1, 106-122 (1995); Prevalence of Lysosomal Storage Disorders, Peter J. Meikle et al. , Jama, Vol. 281, No.3, 249-254 (1999); Cellular Pathology of Lysosomal Storage Disorders, Sidney Weisner, Rose F. Kennedy, Brain Pathology, vol. 8, 175-193 (1998). Applicant also directs the Examiner's attention to the citation and abstracts of 48 items obtained from a search of PubMed for publications prior to the application's filing date having "lysosomal storage disorders" in the title. Applicant respectfully traverses this rejection and asserts that the rejection of claims 9-14 under 35 U.S.C. §112, second paragraph be withdrawn.

New Claim 25

Applicant has added new claim 25. New claim 25 is identical to originally filed claim 9. As such, new claim 25 adds no new matter and is fully supported by the application as filed.

Applicant notes that claim 25 is directed toward treating neurodegeneration. Treatment of neurodegeneration is disclosed in the as filed specification, for example, at page 8, lines 19 – 21 ("Lysosomal modulation, thus, provides a treatment for neurodegenerative events including those underlying Alzheimer's disease, Parkinson's disease, and lysosomal storage disorders.")

In summary, the Applicant has addressed each of the rejections within the present Office Action. It is believed the application now stands in condition for allowance, and prompt favorable action thereon is respectfully solicited.

Respectfully submitted,

Ben A. Bahr

By: _____
James E. Piotrowski
Registration No. 43,860
Alix, Yale & Ristas, LLP
Attorney for Applicants

Date: 12-28-2004
750 Main Street- Suite 1400
Hartford, CT 06103-2721
(860) 527-9211

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